left the circulation and is fixed to tissue is not inactivated, and no therapeutic agent has been identified that will interrupt the action of fixed toxin on tissue. Therefore, delayed therapy may not be effective.

2. Diphtheria antitoxin, comprising serum from horses immunized against the toxin, produces frequent symptomatic and occasional fatal hypersensitivity reactions.

Recommendations

1. The limited therapeutic effectiveness of diphtheria antitoxin and doubts about its prophylactic efficacy plus the success of widespread active immunization of populations indicate the need to intensify the efforts toward active immunization of as many individuals as possible. Therefore, it is recommended that support for widespread public immunization programs be augmented. Such preventive programs are far more effective in reducing morbidity and mortality from diphtheria than is antitoxin, whether used therapeutically or prophylactically. A widely immunized population would tend to eliminate the use of antitoxin and its attendant risk. (See Generic Statement on Diphtheria Toxoid and Tetanus and Diphtheria Toxoids for Adult Use (Td).)

2. Because passive immunization is still required for treatment of diphtheria in unimmunized individuals and occasionally in those apparently adequately immunized, consideration should be given to the development of diphtheria immune globulin of human origin.

3. Further information should be obtained regarding the possibility of a significant reduction in the reactivity of animal serum.

Basis for Classification

In the absence of controlled studies, difficult to obtain with this now rare life-threatening disease, the Panel could not insist on such evidence of efficacy. There is a sufficient body of historical data suggesting that diphtheria antitoxin is of some effect, albeit marginal, in the treatment and prophylaxis of diphtheria to justify classification in Category I.

Bibliography

See Bibliography for Diphtheria Toxoid.

SPECIFIC PRODUCT REVIEWS

Diphtheria Antitoxin Manufactured by Bureau of Laboratories, Michigan Department of Public Health

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Antitoxin Manufactured by Istituto Sieroterapico Vaccinogeno Toscano Sclavo

1. *Description.* This diphtheria antitoxin is prepared from the plasma of horses hyperimmunized against diphtheria toxin. The plasma is semirefined by a process of enzymatic action, ammonium sulfate precipitation, heat, and dialysis. The final product is sterilized by Millipore filtration and metacresol is added as a preservative to a concentration of 0.3 percent. The final product is marketed in 10,000 and 20,000 unit vials; the concentration is not specified.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the treatment of diphtheria and for the prevention of diphtheria in contacts who have not been previously immunized. For prevention, 10,000 units injected intramuscularly is recommended. For treatment, between 20,000 and 120,000 units, administered as a single dose, is recommended, with the larger doses being given to patients with more severe disease or disease of longer duration. It is recommended that approximately half of the dose be given intravenously and the rest intramuscularly.

Appropriate warnings are given about horse serum sensitivity and recommendations for intracutaneous or conjunctival testing for sensitivity are made. A satisfactory schedule is provided for the administration of antitoxin to individuals who display a positive sensitivity test. It is also stated that such individuals should not recieve intravenous antitoxin.

b. *Contraindications.* The only contraindication listed is an intravenous injection to individuals with a postive sensitivity test.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are cited. Only general comments about confirmation of the efficacy of the product by results obtained in Italy and elsewhere since 1956 are stated in the manufacturer's submission to the Panel (Ref. 1).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* It is stated that many thousand vials have been distributed in the past 5 years without significant complaints regarding reactions.

c. *Benefit/risk ratio.* The methods of manufacture and the distribution of this antitoxin over the years indicate that it is comparable to other diphtheria antitoxins. The benefit-to-risk assessment of this product appears to be satisfactory for reasons cited in the Generic Statement.

4. *Critique.* This is an equine diphtheria antitoxin made according to accepted standards. It would appear to be as safe and as effective as any diphtheria antitoxin.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be contained with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Diphtheria Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Diphtheria Antitoxin Manufactured by Massachusetts Public Health Biologic Laboratories

No data have been provided by the manufacturer for diphtheria antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Diphtheria Antitoxin Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* Diphtheria antitoxin, U.S.P., as produced by Merrell-National Laboratories, is prepared from the

plasma of horses hyperimmunized with both diphtheria toxoid and toxin. The antitoxin content of the plasma is concentrated by ammonium sulfate precipitation and refined by partial pepsin digestion. The final diluent is physiologic saline and the preservative is 0.4 percent tricresol. The antitoxin is packaged in 20,000 unit vials with a concentration of at least 500 units per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the treatment of diphtheria and for prevention of diphtheria in exposed, susceptible individuals. The recommendations for its therapeutic use are complete, includings precautions, appropriate regimens for sensitivity testing and desensitization, dosage schedules, and the necessity for antimicrobial therapy.

Recommendations for prophylactic use in all exposed, susceptible individuals include sensitivity precautions, dosage, and emphasize subsequent active immunization. Serum sickness is described as a side effect. The package label is quite satisfactory.

b. *Contraindications.* None is specified, and it is stated that in individuals with diphtheria, antitoxin is mandatory.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Potency tests in animals are conducted according to Federal regulations.

(2) *Human.* No specific data are cited. The manufacturer states that early files on this product are no longer available. Excerpts from standard literature relating to diphtheria antitoxin are provided in the submission to the Panel (Ref. 2).

b. *Safety*—(1) *Animal.* This product is tested for total cresol, and for solids, pyrogenic activity, and sterility according to Federal regulations.

(2) *Human.* No information is provided other than the absence of any reported medical complaints during the past 5 years, during which time thousands of doses were distributed.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory for reasons cited in the Generic Statement.

4. *Critique.* This product is still needed because of incomplete immunization of the U.S. populations and the continuing presence of diphtheria, and because a preparation produced in humans is not available. The package insert should reflect the preferability of erythromycin, lincomycin, or penicillin over antitoxin for prevention of diphtheria in exposed, susceptible individuals.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

References

(1) BER volume 2112.
(2) BER volume 2075.

Generic Statement

Gas Gangrene Antitoxin

Gas gangrene is a serious and often fatal anaerobic infection of soft tissue, muscle, and sometimes blood. It is best known as a dreaded complication of injuries to soldiers in wartime, but occasionally occurs among civilians in peacetime following trauma, or occasionally following surgery.

The etiologic agents of gas gangrene are the so-called "histotoxic" clostridia, including *Clostridium perfringens, Clostridium novyi, Clostridium septicum, Clostridium histolyticum, Clostridium bifermentans,* and *Clostridium fallax. Clostridium perfringens* is the most commonly recovered and the best studied. All of these organisms require nearly complete anaerobiosis and a reduced oxidation-reduction potential for growth. In common with other clostridia such as *Clostridium tetani,* the histotoxic clostridia are widely distributed in nature, being readily found in the gastrointestinal tract of man and animals, as well as in soils.

It is generally believed that the various toxins produced by the histotoxic clostridia account for their rapid spread in tissue, and for the profound toxemia that is such a prominent part of the clinical picture of gas gangrene. Each species produces a number of extracellular toxins, including lecithinases, collagenases, proteinases, and deoxyribonucleases. The most widely studied of these toxins has been the alpha toxin of *Clostridium perfringens,* a lecithinase that injures cell membranes and alters capillary permeability. Although the activities of a few of these toxins have been carefully defined, the cause of the profound toxemia and extreme morbidity that accompanies clinical gas gangrene remains unclear. In addition to the toxins themselves, the toxemia has been attributed to release of the products of tissue necrosis, interference with enzyme systems, and the profound acidosis.

Active immunization using toxoids prepared from the histotoxic clostridia has not proven practicable on a large scale. When such toxoids are used to hyperimmunize horses, however, antitoxic activity does develop. Equine antitoxin has therefore been used in passive immunization in humans, both in the prophylaxis and treatment of gas gangrene.

Nature of the Product

Polyvalent gas gangrene antitoxin is a preparation of hyperimmune serum from horses immunized against gas gangrene toxins.

Production

Gas gangrene polyvalent antitoxins are produced from plasma of hyperimmunized horses. The crude plasma/saline mixture, at a pH of 3.9, is treated with pepsin and ammonium sulfate. "Digestion" is continued for 24 to 48 hours, at which time 75 to 80 percent of the protein will not coagulate on boiling. The material is filtered, the protein in the filtrate is precipitated by ammonium sulfate, and the precipitate is washed and suspended in phenolyzed distilled water with toluene and chloroform as additional preservatives. The resultant material contains mainly gamma and beta globulins.

The final product is diluted with sodium chloride solution and preserved with 1:20,000 phenylmercuric borate plus approximately 0.4 percent phenol. Each vial of the final product contains 10,000 units *Clostridium perfringens* antitoxin, 10,000 units *Clostridium septicum* antitoxin, 3,000 units *Clostridium histolyticum* antitoxin, 15,000 units *Clostridium novyi* antitoxin, and 15,000 units *Clostridium bifermentans antitoxin.*

Use and Contraindications

The main purpose of the administration of polyvalent gas gangrene antitoxin is to prevent death from toxemia in established cases of clostridial infection, and is therefore an adjunct to adequate surgery.

The recommended dosage schedule is approximately 50,000 units (2 vials) every 4 to 6 hours before or after surgery for a period of 24 to 48 hours. Administration is normally via the intravenous route, but it may be used intramuscularly as well.

It must be emphasized that prompt and adequate surgical debridement is the sine qua non in therapy of gas gangrene. Important adjunctive measures include careful management of fluid and electrolyte balance, and prompt antibiotic therapy, including large doses of penicillin G. Serotherapy with polyvalent gas gangrene antitoxin and hyperbaric oxygenation have been considered adjunctive measures whose relative merits are not clear.

Gas gangrene antitoxin is contraindicated in individuals with a

history of sensitivity to horses, horse dander, or horse serum, and should be given with extreme caution to anyone who has previously received any injections containing horse serum.

Safety

Federal regulations specify that polyvalent gas gangrene antitoxin must be tested to ensure sterility and contain an appropriate preservative in specified amount. The product must meet prescribed tests for freedom from pyrogenicity.

The most significant problem regarding the safety of polyvalent gas gangrene antitoxin relates to sensitivity to horse serum. Two types of hypersensitivity reactions occur—anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by desensitization. Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization within a few minutes following injection, and most characteristically include cardiovascular collapse and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more of cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. The larger the dose of serum, the more likely is serum sickness to occur. The major manifestations of serum sickness are fever, arthritis, lymphadenopathy, and urticaria. Symptoms persist for days or weeks. Fatalities are rare, except in instances of laryngeal edema. Rates of serum sickness following horse serum vary and are directly dose dependent. The frequency is approximately 1 percent per 1 mL of serum.

Efficacy

The efficacy of polyvalent gas gangrene antitoxin has been extraordinarily difficult to assess with precision, owing to the fact that it is at best an adjunct in the management of gas gangrene.

For the prophylactic treatment of gas gangrene following traumatic injuries there is general agreement that polyvalent gas gangrene antitoxin is of no value. The work of MacLennan and MacFarlane, who studied the occurrence of gas gangrene among British troops during World War II, suggested that the incubation period of the disease might be lengthened by the administration of gas gangrene antitoxin, but clear evidence of efficacy in prophylaxis of gas gangrene cannot be found.

The mainstay of therapy of gas gangrene has been and continues to be prompt surgery that includes complete removal of all infected tissue. Therapeutic regimens that have stopped short of such radical surgery have invariably failed, regardless of other adjunctive measures utilized. The adjunctive measures most often utilized include careful management of fluid and electrolyte balance, prompt antibiotic therapy, including large doses of penicillin G, passive immunization with polyvalent gas gangrene antitoxin, and hyperbaric oxygenation.

The best available data in support of therapeutic efficacy of polyvalent gas gangrene antitoxin derived from the British experiences in World War II, as summarized by MacLennan and MacFarlane. These studies were obviously not designed as rigidly controlled field trials, but did not evidence that the combined use of surgery and antitoxin was approximately 40 percent more effective than surgery alone.

Data on the efficacy of antitoxin in the treatment of gas gangrene since World War II is scanty at best, wholly uncontrolled, and consists mostly of individual case reports or small series of cases.

Although it is difficult to dismiss entirely the experiences recorded by MacLennan, who felt that passive immunization with gas gangrene antitoxin was of distinct benefit in the management of gas gangrene, its role in management remains uncertain. Some or all of its apparent effectiveness during **World War II may now have been minimized or eroded completely by** emphasis on early diagnosis, prompt surgery, and other adjunctive and supportive therapy including antibiotics.

Current surgical opinion reflects these uncertainties. The manual "Control of Infection in Surgical Patients," edited by Altemeier, Burke, Pruitt, and Sandusky, states simply "gas gangrene antitoxin has been found to be of little or no value in the prevention of clinical gas gangrene."

Special Problems

The major special problem identified is the lack of acceptable evidence of **efficacy of polyvalent antitoxin in the management of clinical gas gangrene. The Panel sees no likelihood that such evidence will be forthcoming in the foreseeable future.**

A second major problem in the evaluation of this product is the **apparent lack of standardization of antitoxin unitage. International Units of antitoxin are defined so that no two represent the same protective power, i.e., *Clostridium novyi* is approximately 100 times greater than *Clostridium perfringens*, and *Clostridium bifermentans* is approximately 50 times greater than *Clostridium perfringens*. The protective power of "one vial" of the Lederle Laboratories Division's polyvalent gas gangrene antitoxin (pentavalent) in terms of mouse minimum lethal dose of toxin would be as follows:**

Clostridium perfringens	500,000 to 700,000
Clostridium septicum	400,000 to 640,000
Clostridium histolyticum	approx. to 135,000
Clostridium novyi	approx. to 7,500,000
Clostridium bifermentans	2,850,000 to 5,700,000

Another aspect of this problem relates to the quantity of each of the antitoxins packed in a vial. This problem is illustrated in Table 1.

Recommendations

The Panel recommends that further research be encouraged on the nature of the toxins produced by the histotoxic clostridia, and the mechanism of action of their effects on mammalian tissue.

Basis for Classification

In the judgment of the Panel, there is not adequate evidence of efficacy of polyvalent gas gangrene antitoxin when used as recommended in either the prophylaxis or therapy of gas gangrene. Therefore, for this reason the Panel recommends that this product be classified in Category IIIB.

TABLE 1—ANTITOXIN CONTENT (INTERNATIONAL UNITS)

Author/Manufacturer	C. perfringens	C. septicum	C. novyi	C. histolyticum	C. bifermentans	Recommended dose
MacLennan (Ref. 1), MacFarlane (Ref. 2)/Medical Research Council.	7,500	3,750	2,500	—	—	>116,500 units (1 vial).
Gledhill/Burroughs Welcome	9,000	4,500	3,000	—	—	3 vials.
Lindsey (Ref. 3), United States National Standard; Lederle.	9,000	4,500	9,000	—	—	12 mL/vial, dose not stated.
Present product/Lederle	10,000	10,000	1,500	3,000	1,500	2 vials.

References

(1) MacLennan, J.D., "Anaerobic Infections of War Wounds in the Middle East," *The Lancet*, 2:123–126, 1943.

(2) MacFarlane, M.G., "The Therapeutic Value of Gas-Gangrene Antitoxin," *British Medical Journal*, 2:636–640, 1943.

(3) Lindsey, D., H.M. Wise, A.T. Knecht, and H.E. Noyes, "Influenza of Route of Administration on Effectiveness of Clostridial Antitoxin," *American Medical Association Archives of Surgery*, 78:328–330, 1959.

SPECIFIC PRODUCT REVIEWS

Gas Gangrene Polyvalent Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Company

1. *Description.* Gas gangrene polyvalent antitoxins are produced from plasma of hyperimmunized horses. After the antitoxin plasma is "refined and concentrated," it is diluted with sodium chloride solution and preserved with 1:20,000 phenylmercuric borate plus approximately 0.4 percent phenol. Each vial contains: 10,000 units *Clostridium perfringens*, 10,000 units of *Clostridium septicum*, 3,000 units of *Clostridium histolyticum*, 1,500 units of *Clostridium novyi*, and 1,500 units of *Clostridium bifermentans* antitoxin.

The refining process involves pepsin/ammonium sulfate treatment of a crude plasma/saline mixture (pH 3.9). "Digestion" is contained for 24 to 48 hours, at which time 75 to 80 percent of the protein will not coagulate on boiling. The material is filtered, the protein in the filtrate is precipitated by ammonium sulfate, the precipitate is washed and suspended in phenolyzed distilled water with toluene and chloroform as additional preservatives. The resultant material contains mainly gamma and beta globulins.

2. *Labeling*—a. *Recommended use/indications.*

* * * to prevent death from toxemia in an established or suspected case of clostridial infection until adequate surgery and antibiotic therapy can bring the infection under control. The usefulness of this antitoxin to prevent clostridial infection is controversial but is generally considered to be of little or no value when given prophylactically.

The recommended dosage schedule is approximately 50,000 units (2 vials) every 4 to 6 hours before or after surgery for a period of 24 to 48 hours. Administration is normally intravenous, but it may be used intramuscularly.

b. *Contraindications.* Sensitivity to horse serum, history of asthema angioneurotic edema, or other allergy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

Lindsey (Ref. 1) has demonstrated efficacy in extensively wounded goats when massive doses of trivalent antitoxin were employed, approximately 1,800 to 2,600 units of *Clostridium perfringens* antitoxin per kg.

(2) *Human.* The best available data derived from the British experience in World War II.

(i) MacLennan (Ref. 2) demonstrated the following:

Drug therapy	No antitoxin		Antitoxin[1]		
	Cases	Death	Cases	Death	Differences
Sulfonamides	28	22 (79%)	58	19 (33%)	46%.

[1] The average dose for survivors treated with antitoxin was 40,000 to 50,000 units. The composition of the antitoxin is not defined, but it is assumed to be that recommended by the Medical Research Council with 1 therapeutic dose containing 7,500 international units *Clostridium perfringens antitoxins, 3,750 international units of Clostridium septicum*, and 2,500 international units of *Clostridium novyi*.

(ii) MacFarlane (Ref. 3) analyzed reports to subcommittee on anaerobic wound infections. The reports came from multiple sources between 1940 and 1943. Of 165 cases (not including those of MacLennan), 139 were classified as "toxic cases"; some received antitoxin, others had not. Results were as follows:

No antitoxin		Antitoxin		Difference
Cases	Death	Cases	Death	
25	21 (84%)	114	58 (51%)	33%

From these studies they concluded that the combined use of surgery and antitoxin was more effective than surgery alone.

(iii) The MacLennan and MacFarlane studies which suggested effectiveness of gas gangrene antitoxin used preparations which differed in composition and which were administered in differing dosages. The Lederle gas gangrene antitoxin differs in composition from those used by both MacLennan and MacFarlane.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Most reports contain no data on reactions; however, serum sickness would be anticipated. Frequency would be approximately 1 percent per 1 mL of serum.

c. *Benefit/risk ratio.* Benefit-to-risk considerations with reference to this product are not acceptable.

4. *Critique.* Major problems in the evaluation of this product have been discussed in the Generic Statement. The product is poorly standardized, and there is not adequate evidence of efficacy when used as recommended in either the prophylaxis of treatment of gas gangrene.

5. *Recommendations.* The Panel recommends that this product be classified as Category IIIB, and that the appropriate license be revoked owing to the lack of acceptable evidence of efficacy.

Tetanus and Gas Gangrene Polyvalent Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

References

(1) Lindsey, D., H. M. Wise, A. T. Knecht, and H. E. Noyes, "Influence of Route of Administration of Effectiveness of Clostridial Antitoxin," *American Medical Association Archives of Surgery*, 78:328–330, 1959.

(2) MacLennan, J. D., "Anaerobic Infections of War Wounds in the Middle East," *The Lancet*, 2:123–126, 1943.

(3) MacFarlane, M. G., "The Therapeutic Value of Gas-Gangrene Antitoxin," *British Medical Journal*, 2:636–640, 1943.

Generic Statement

Pertussis Immune Globulin (Human)

The pathogenesis, symptomatology, complications, and epidemiology of pertussis and its prevention with killed-bacterial vaccine have been described previously in this Report.

Serum therapy was initiated in the 1930's and early reports on the effect of convalescent human sera and hyperimmune animal sera in prophylaxis and therapy of pertussis were quite favorable. Subsequently a refined product, gamma globulin of human origin, was introduced and was similarly accepted enthusiastically. Later controlled studies failed to demonstrate significant benefit.

Several factors may influence the effect of antibody therapy: (1) The site

of the infection and access of antibody to the site; (2) whether antiserum alters the pathophysiologic effects of the organisms' reactive factors; and (3) the classes of immune globulin in convalescent serum which presumably contribute to recovery.

Description

Pertussis immune globulin is predominantly the immunoglobulin fraction from a pool of serum from human donors who have been hyper-immunized with pertussis vaccine. Earlier the product was sometimes obtained from persons who were hyperimmunized with vaccine following recovery from pertussis.

Production

The source of this product is plasma from adults who have been repeatedly immunized with pertussis vaccine. This pertussis immune globulin is diluted with normal human immunoglobulin to achieve a standard concentration of protein. The donors are required to be free of causative agents of diseases that are not destroyed or removed by the processing methods, as specified by Federal regulations.

The plasma is fractionated by a cold alcohol method, yielding a preparation with over 90 percent of IgG. Thimerosal in dilution 1:10,000 may be added as a preservative. Pertussis immune globulin is submitted to standard tests for purity, sterility, safety, and protein content according to Federal regulations. Up to this time there has been no standard of potency which has been correlated with human efficacy. The two products licensed in the United States at the present time are compared in an in vitro agglutination test to a reference serum.

Use and Contraindications

The product has been recommended for intimately exposed children under 2 years of age who have not been vaccinated. The dose recommended by manufacturers is 1.25 to 1.5 mL intramuscularly, repeated in 5 to 7 days if exposure continues.

For treatment of infants with pertussis 1.25 mL intramuscularly for 3 to 5 doses, or 3 to 6.75 mL as a single dose is recommended. The product should not be administered intravenously.

Expert opinions as to the usefulness of pertussis immune globulin both in treatment and prophylaxis diverge. Thus the 1975 report of the American Public Health Association states that passive immunization is of no value in treatment or in prevention. However, the American Academy of Pediatrics which previously accepted its use in prophylaxis, in 1977 states that "There is no convincing evidence that Pertussis Immune Serum Globulin (Human) has any efficacy in preventing or treating pertussis, and its use is not recommended."

The product is contraindicated in individuals who are known to have an allergic response to immunoglobulin. Epinephrine should be at hand for treatment of rare reactions.

Safety

This product must meet Federal regulations as to safety. Adverse reactions to immune globulins are rare, and consist of anaphylactic and allergic reactions. The greatest risk consists of inadvertent intravenous injection of aggregated immunoglobulin which leads to shock.

Manufacturers are required to record reported reactions.

Efficacy

The use of pertussis immune globulin is empirical, because the nature of the protective factor in human serum is not known. However, the agglutinating antibody and/or a bactericidal antibody may play a role in protection. Furthermore, it is not clear whether protective factors are present in the IgG fraction. Some speculate that protection is located in the IgM fraction, because infants do not appear to obtain passive immunity from their mothers. Since *Bordetella pertussis* infection is primarily an infection of the bronchial epithelium, it is also possible that the protective factor is located in the IgA fraction of the immunoglobulins. Pertussis immune globulin (human) can protect mice under experimental conditions, but its relation to human efficacy has not been determined.

Studies conducted in the 1930's and 1940's when pertussis was still a virulent disease with a relatively high mortality rate suggested a prophylactic and therapeutic effect from convalescent human sera and animal hyperimmune sera. Unfortunately, these studies were not adequately controlled and comparison groups outside the experimental setting were often utilized.

In the last decades, a few controlled studies have been conducted with pertussis immune globulin. They did not demonstrate statistically significant differences between treatment and control groups. However, concurrent antimicrobial therapy may have masked any beneficial effect; it is also possible that the specific lots and dosage used were ineffective, and the numbers of study subjects were too few. At least in one study the dose was lower than the recommended one. Also, the stage of disease when the product was given has varied and the methods of allocation to study groups have not always been clearly described.

During the last decades, erythromycin and ampicillin have become the preferred methods for prophylaxis and treatment of pertussis.

Special Problems

1. Several studies, not adequately controlled, conducted in the 1930's and 1940's when pertussis was a more prevalent and virulent disease, provided evidence of therapeutic and prophylactic benefit from convalescent serum, human hyperimmune serum and rabbit hyperimmune serum. The initial experience with pertussis immune globulin (human) suggested similar effects, but more recent, well-controlled studies did not confirm this suggestion. Whether this indicates that alcohol fractionation of plasma in the preparation of immunoglobulin eliminates other protective components in unknown. It appears, however, that there is little evidence of efficacy of the current product.

2. No animal model or other laboratory technique for evaluation of potency has been directly related to efficacy in humans. The only animal model employed utilized intracerebral injection of *Bordetella pertussis* bacteria into mice; a protective effect of pertussis immune globulin can be demonstrated. Other potentially useful models such as intranasal challenge of mice have been insufficiently studied.

3. Knowledge of the immune mechanisms to pertussis in humans, particularly as to class of immunoglobulin, and the role of humoral immunity, especially the role of bacteriocidal antibody, is rudimentary. The role of cell-mediated immunity is unknown.

4. Whereas the product appears relatively safe for the recipient, the practice of hyperimmunizing the donors with pertussis vaccine is not without risk.

Recommendations

1. The available information is insufficient to classify pertussis immune globulin as effective. Further studies are required before such a decision can be made.

2. The Panel recommends that research be directed to identify the mechanism by which immunity to pertussis is acquired. Identification and characterization of protective antibodies, if such are present, are imperative to determine the value of pertussis immune globulin as presently constituted. Studies are also necessary